a6

--78. The method of claim 48, further comprising (d) sonicating the particles until particles of the desired size are obtained.--

REMARKS

I. PENDING CLAIMS AND SUPPORT FOR AMENDMENT

Upon entry of the present amendment, claims 1-3, 7-8, 12-24, 40-43, 47-53, 57, 62-65, and 77-78 will be pending in the application. Claims 4-6, 9-11, 26-39, 44-46, 54-56, 58-61, 66-76 have been canceled without prejudice or disclaimer to the subject matter thereof. Upon entry of the present amendment, claims from Groups I-III remain pending in the application. Note that Applicant has incorporated claims from Group VII into the claims of Group I . Applicants have also added new claim 78. Support for this new claim appears in the specification at page 21.

II. REQUIREMENT FOR RESTRICTION

The Examiner required restriction between Groups I-VII, and Applicants elected the claims of Group I, with traverse. The Examiner maintains that the inventions of each group represent a patentably distinct invention, each having differing chemical, biochemical, and immunological properties and differing issues regarding enablement, and has withdrawn claims 4-16, 19-39, 44-46, 51-53, 54-56, 58-61, and 66-76 from consideration. Applicants respectfully re-traverse this restriction and request reconsideration and withdrawal thereof.

At least with respect to Groups I-III, Applicants traverse this requirement because the term "antigenic" includes viral, bacterial, and fungal proteins. The

definition of the term "antigen" means "a substance that causes the formation of an antibody or elicits a cellular response." *See* Harcourt Academic Press Dictionary of Science and Technology. Because the definition of antigenic includes any substance to which the body reacts by producing antibodies, searching antigenic viral, bacterial, and fungal proteins does not present an undue burden on the Examiner since the Examiner would have to search and examiner "antigenic material" with the elected invention.

Additionally, in an effort to move the application toward allowance, Applicants have incorporated the limitations of the claims of Group VII (directed to calcium phosphate particles complexed with surface modifying agents and methods for making said particles) into the claims of elected Group I. Applicants submit that the surface modifying agents act, at least in part, to help the at least partial coating of the antigenic material adhere to the particle.

III. REJECTIONS UNDER 35 U.S.C. § 112

Claims 3, 17-18, 47-50, 53, 57, and 65 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

A. Claims 3, 50, 53, and 57.

The Examiner asserts that the use of the term "partially coated" renders claims 3, 50, 53, and 57 vague and indefinite. The Examiner asks what percentage of the particle must be coated for it to be considered "partially coated" as opposed to

"uncoated" or "coated," and whether the coating must be equally dispersed over the particle or localized in a given region of the particle.

Applicants assert that the Examiner in not considering the terminology "partially coated" in context. "At least partially coated" means that the claims cover particles that are completely coated, as well as those that are not completely coated, but that have some coating. In other words, as long as the particle has some antigenic material on its surface, it would be considered "partially coated" The term "at least partially coated" is sufficiently clear to provide the metes and bounds of the claimed invention.

B. Claim 17.

Claim 17 has been corrected to clarify that "peptides of a virus" is a separate group from "functional proteins."

C. Claim 47.

The Examiner asserts that the use of the term "reacting" is vague and indefinite. The Examiner queries whether Applicants mean that the two salts are admixed or whether there are other steps involved. One of ordinary skill in the art would recognize that mixing a calcium salt with a phosphate salt will lead to calcium ions combining ("reacting") with phosphate ions to form a relatively insoluble precipitate of the particles of the present invention. Thus, any combining of a soluble calcium salt with a soluble phosphate salt to form the particles of claim 1 would infringe claim 47, and the metes and bounds of claim 47 are clear and not indefinite.

D. Claim 53.

Claim 53 has been amended to incorporate the limitations of the parent claim.

IV. REJECTIONS UNDER 35 U.S.C. § 102(b)

Claims 1-3, 17, 40-43, 47-48, 53, 62-65 and 77 are rejected under 35 U.S.C. § 102(b) as being anticipated by Relyveld (U.S. Patent No. 4,016,252). Applicants respectfully traverse this rejection and request reconsideration and withdrawal thereof.

The Examiner has characterized Relyveld as disclosing an aqueous gel of calcium phosphate useful for preparation of adsorbed vaccines, prepared by contacting an antigen with the aqueous gel, as well as methods of making the gel in combination with viral vaccines as an adjuvant. The Examiner states that Relyveld discloses the claimed particle sizes, but concedes that Relyveld does not disclose particles that are "substantially smooth" or "substantially spherical." The Examiner states, however, that in the absence of factual evidence to the contrary, because the prior art particles have the composition and size of the claimed particles, they anticipate the claimed invention.

Applicants respectfully traverse this rejection. First, MPEP §2131 requires that to anticipate a claim, the reference must teach *every element* of the claim. (emphasis added). "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *See Verdegaal Bros. V. Union Oil Co. of Calif.*, 814 F.2d 628, 631 (Fed.

Cir. 1987). The fact that the Relyveld particles have a certain composition and size or that they are "colloidal" simply does not anticipate "substantially smooth" particles. There is no disclosure in Relyveld of the particles having a particular morphology, other than the statement that the gel exhibits a "colloidal character." The Examiner cites a definition of "colloid" meaning "a substance consisting of very tiny particles that are usually between 1 nanometer and 1000 nanometers in diameter and are suspended in a continuous medium . . . ." In other words, the particles are not readily filtered out from the gel. The term "colloidal" does not mean or infer a "substantially smooth" particle.

Relyveld also states that the "particles of special calcium phosphate of the present invention are considerably finer than those hitherto known and used calcium phosphate gels." The particles of the suspension should be as fine as possible, which requirement is well met by the gel because it "exhibits a marked colloidal character." In other words, Relyveld attributes the colloid character of its gel to the fact that the velocity of settling of the gel is slower than that of conventional calcium phosphate gel. Relyveld uses the term "colloidal character" to mean that its particles are so fine that they remain suspended in a continuous medium, not to refer to their morphology.

Furthermore, there is no basis for presuming that the particles of the claimed invention would inherently form in the gel of Relyveld, since the particles themselves, as well as methods of making these two materials, are so different. Relyveld discloses mixing the components of its gel very rapidly to obtain a precipitate that is

"richer in calcium than theory would indicate." Relyveld then emphasizes a quick adjustment of the pH of the mixture. After the mixture is allowed to stand, a gel separates from the liquid, and all of the initial calcium is found in the phosphate precipitate while a portion of the phosphate ions remain in solution in the clear liquid. The gel is purified by washing to remove the phosphorous ions, which may inhibit adsorption of certain antigens, and then sterilized so that it can be used as an adsorbent for various antigens.

Relyveld's rapid formation would change the size of the particles and cause them to be larger than the particles of the presently claimed invention. Additionally, Relyveld also emphasizes - and recites in its claims - specific ratios of calcium to phosphate. The high molar concentration of its reactants will cause the gel of Relyveld to be highly amorphous, also resulting in particles that are larger than those of the presently claimed invention.

Additionally, because the particles of Relyveld serve a different function than those of the present invention, there is a distinct difference in the resulting particles. First, the Relyveld particle are for *adsorbing* vaccines, whereas the presently claimed particles are for *adjuvanting* vaccines. Claim 1 has been amended to clarify this distinction. "Adsorbing" refers to the process of attracting and holding molecules of another substance to the surface of its molecules. *See* On-line Medical Dictionary at http://www.graylab.ac.uk/cgi-bin/omd?adsorb. "Adjuvanting" refers to adding a substance to a vaccine to improve the immune response so that less vaccine is needed

to produce a nonspecific stimulator of the immune response. *See* On-line Medical Dictionary at http://www.graylab.ac.uk/cgi-bin/omd?adjuvant. To adsorb a vaccine, the antigenic material must be adhered to the particles, whereas to adjuvant a vaccine, the particle itself need merely speed the action of the vaccine. The particles of the present invention may be used alone to adjuvant a vaccine, or may have material added thereto to achieve enhanced results, but they are not made as a calcium phosphate gel for adsorbing vaccines, as disclosed by Relyveld.

Relyveld consistently describes its particles as useful for the preparation of adsorbed vaccines. If the antigens are adsorbed on the particles, they must accumulate on and be attached to the surface of the particles. Relyveld describes a series of washing steps, which allows the particles in the gel to better adsorb antigens. In Example 1, Relyveld describes adsorbing antigens to the particle. After 3 successive adsorptions of vaccine, "the supernatant was always inactive which proves that the vaccine had been completely adsorbed."

On the other hand, in claim 3, where Applicant recites that antigenic material is added to the particle, the antigenic material "at least partially coats" the particles, meaning that there may be some material free-floating in solution. Applicant does not use any washing steps. The material (such as antigens, immunoenhancing factor, polynucleic acid, etc.) that Applicant puts into the admixture is not washed out.

Relyveld also indicates that "purification of the gel of the calcium phosphate is of great importance" and that "the phosphorous ions in the solution inhibit adsorption

of certain antigens." On the other hand, Applicants form an admixture that does not require purification. The antigens in its solution are available for immediate use upon administration.

Furthermore, discussion of and claims directed to the use of Applicants' particles as vaccine adjuvants means that material is not required to be bound to the particle. When Applicant adds antigenic material to the particle, as recited in claims 3 and 65, the attached material allows controlled release of the bound material. The free-floating material is available to the system immediately. In other words, much of the material is juxtaposed to the particles in solution and not necessarily bound to the particle and not washed out.

V. REJECTIONS UNDER 35 U.S.C. § 103(a)

Claims 1-3, 17, 18, 40-43, 47-48, 62-65 and 77 are rejected under 35 U.S.C. § 103(a) as being obvious over Relyveld in view of Kossovsky (U.S. Patent No. 5,462,750). Applicants respectfully traverse this rejection and request reconsideration and withdrawal thereof. To the extent that the Examiner relies on Relyveld in this rejection, Applicants incorporate the comments provided above.

The Examiner concedes that Relyveld does not disclose the use of EBV, HIV, HPV, HSV, pox or influenza viral proteins as the previously described antigenic material, but asserts that Kossovsky et al. disclose biologically active particles with diameters of less than 1000 nm which are coated with various viral proteins and that suitable sources for the viral proteins include EBV, HIV, HPV, HSV, and pox viruses.

The Examiner asserts that the particles disclosed by Relyveld and Kossovsky are similar with regard to size and function, it would have been obvious to use the viral proteins of Kossovsky with the particles of Relyveld.

First, the functionalities of the particles of Relyveld and Kossovsky are completely different, and there would be no motivation to combine the two references. As described above, Relyveld provides a gel for adsorbing vaccines. Kossovsky, on the other hand, provides a viral decoy. Kossovsky specifies the use of a particle having a size that mimics the DNA or RNA core. Viral peptides are attached to the core to mimic the native virus. When the viral protein is attached to the microparticle core, the result is a decoy virus which may be used as a vaccine, diagnostic tool, or antigenic reagent for raising antibodies. *See* col. 3, ll. 31-34. One of ordinary skill in the art wishing to prepare a gel for adsorbing vaccines would not be led to a reference that discloses viral decoys.

Furthermore, the preparations disclosed by the two references are completely different. Kossovsky prepares particles using plasma-assisted chemical vapor deposition (PACVD) functioning at high atmospheric pressures, *see* col. 4, ll. 47-53, whereas Relyveld using a series of rapid mixing followed by pH adjustments. Kossovsky also coats its particles with a specific binding material, whereas Relyveld does not suggest this method.

CONCLUSION

Applicant respectfully submits that, when the arguments and evidence are properly considered, the necessary conclusion is that the presently claimed invention is not anticipated or obvious over the prior art. Applicant further submits that the present application is in condition for immediate allowance, and an early notification thereof is respectfully requested. If the Examiner believes that further issues remain to be resolved, the Examiner is invited to contact the undersigned at 404.815.6147.

Applicants believes that no fees are due, but if mistaken, please charge any additional fees or credit any overpayment to Deposit Order Account No. 11-0855.

Respectfully submitted,

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